ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 799

[OPTS-42038; BH-FRL 2458-1]

Aryl Phosphates; Response to the Interagency Testing Committee

AGENCY: Environmental Protection Agency (EPA).

ACTION: Advance Notice of Proposed Rulemaking.

SUMMARY: In the Second Report of the Interagency Testing Committee (ITC), transmitted to the Administrator of the EPA on April 10, 1978, the ITC designated the aryl phosphate category for testing consideration. The manufacturers of aryl phosphates are currently conducting a testing program that EPA believes will provide adequate data in some of the areas where the Agency believes testing is needed. For the remaining data gaps, the Agency is publishing this Advance Notice of Proposed Rulemaking (ANPR), which initiates rulemaking to require the testing which appears necessary to complete a preliminary assessment of the health and environmental effects of the aryl phosphates. This notice constitutes EPA's response to the ITC's designation of the aryl phosphates for testing consideration. EPA seeks comment on its conclusions as to the need for further testing of the aryl phosphates and the submission of data, information and views on a number of issues listed in Unit IV under the Supplementary Information heading of this Notice.

DATE: All comments should be submitted on or before February 27, 1984.

ADDRESS: Written comments should bear the document control number OPTS-42038 and should be submitted in triplicate to: TSCA Public Information Office (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Rm. E-108, 401 M St., SW., Washington, D.C. 20460.

The administrative record supporting this action is available for public inspection in Rm. E-107 at the above address from 8:00 a.m. to 4:00 p.m., Monday through Friday, except legal holidays.

FOR FURTHER INFORMATION CONTACT: Jack P. McCarthy, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Environmental Protection Agency, Rm. E-543, 401 M St. SW., Washington, D.C. 20460, Toll Free: (800-424-9065), In Washington, D.C.: (554-1404), Outside the USA: (Operator-202-554-1404).

SUPPLEMENTARY INFORMATION:

I. Background

Section 4(a) of the Toxic Substances Control Act (TSCA) [Pub. L. 94-469, 90 Stat. 2003 *et seq.*, 15 U.S.C. 2601 *et seq.*] authorizes the EPA to promulgate regulations requiring testing of chemical substances and mixtures in order to develop data relevant to determining the risks that such chemicals may present to health and the environment. Section 4(e) of TSCA established an Interagency Testing Committee (ITC) to recommend to the EPA a list of chemicals to be considered for the promulgation of testing rules under section 4(a) of the Act.

On April 10, 1978, the ITC placed on its priority testing list a category of chemicals known as aryl phosphates (see 43 FR 16684, April 19, 1978). The ITC defined "aryl phosphates" as phosphate esters of phenol or of alkyl-substituted phenols. Tri-aryl and mixed alkyl-aryl esters are included, but tri-alkyl esters are excluded. The ITC recommended that the aryl phosphates be considered for testing for the following health effects: carcinogenicity, mutagenicity, teratogenicity and chronic effects (with special emphasis on neurotoxicity). In addition, the ITC also recommended that a epidemiology study be considered because of the large-scale production and potential for substantial occupational exposure to certain aryl phosphates. The ITC also recommended that the aryl phosphates be considered for environmental effects testing and expressed specific concern about the potential for aryl phosphates to persist in the aquatic environment, to bioaccumulate in aquatic species, and the potential effects of aryl phosphates on aquatic and terrestrial systems. This Advance Notice of Proposed Rulemaking provides EPA's response to the ITC's designation of the aryl phosphates as required by TSCA section 4(e).

Under section 4(a)(1) of TSCA, the Administrator shall by rule require testing of a chemical substance to develop appropriate test data if the Agency finds that:

> (A) (i) the manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or mixture, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment,
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> (ii) there are insufficient data and experience upon which the effects of such manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted, and
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> (iii) testing of such substance or mixture with respect to such effects is necessary to develop such data; or
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> (B) (i) a chemical substance or mixture is or will be produced in substantial quantities, and (I) it enters or may reasonably be anticipated to enter the environment in substantial quantities or (II) there is or may be significant or substantial human exposure to such substance or mixture,
>
> (ii) there are insufficient data and experience upon which the effects of the manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted, and
>
> (iii) testing of such substance or mixture with respect to such effects is necessary to develop such data.

EPA uses a weight of evidence approach in making a section 4(a)(1)(A)(i) finding in which both exposure and toxicity information are considered to make the finding that the chemical may present an unreasonable risk. For the section 4(a)(1)(B)(i) finding, EPA considers only production, exposure, and release information to determine if there is substantial production, significant or substantial exposure, and substantial release. Thus, while EPA can require testing for an effect under section 4(a)(1)(A) only if there is a suspicion of a hazard, under section 4(a)(1)(B) EPA can require testing whether or not there are data suggesting adverse effects if the relevant production, exposure, and release criteria are met.

For the findings under both section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii), EPA examines toxicity and fate studies to determine if existing information is adequate to reasonably determine or predict the effects of human exposure to, or environmental release of, the chemical. In making the third finding, that testing is necessary, EPA considers whether ongoing testing will satisfy the information needs for the chemical and whether testing which the Agency might require would be capable of developing the necessary information.

EPA's process for determining when these findings can be made is described

in detail in EPA's first and second proposed test rules as published in the Federal Register of July 18, 1980 (45 FR 48528) and June 5, 1981 (46 FR 30300). The section 4(a)(1)(A) finding is discussed in 45 FR 48528, and the section 4(a)(1)(B) finding is discussed in 46 FR 30300.

In evaluating the ITC's testing recommendations concerning aryl phosphates, EPA considered all available relevant information including the following: information presented in the ITC's report recommending testing consideration; production volume, use, exposure, and release information reported by manufacturers of aryl phosphates under the TSCA section 8(a) Preliminary Assessment Information Rule (40 CFR Part 712); and published and upublished data available to the Agency, including information submitted under the TSCA section 8(d) Health and Safety Data Reporting Rule (40 CFR Part 716).

The nine aryl phosphates listed below have been specifically identified by industry as being constituents of commercial products currently in production.

1. TCP—Tricresyl phosphate, mixed isomers (tritolyl phosphate, CAS No. 1330-78-5).
2. TXP—Trixylenyl phosphate, mixed isomers (trixylyl phosphate, CAS No. 25155-23-1).
3. TPP—Triphenyl phosphate (CAS No. 115-86-6).
4. NPDP—Nonylphenyl diphenyl phosphate, mixed isomers (CAS No. 64532-97-4).
5. DBDP—Dimethylbenzylphenyl diphenyl phosphate, mixed isomers (also known as cumylphenyl diphenyl phosphate, CAS No. 34364-42-6).
6. IPDP—Isopropylphenyl diphenyl phosphate, mixed isomers (CAS No. 28109-99-8).
7. BPDP—Butylphenyl diphenyl phosphate, mixed isomers (CAS No. 34364-42-6).
8. IDPP—Isodecyl diphenyl phosphate (CAS No. 29660-48-3).
9. EHDP—2-Ethylhexyl diphenyl phosphate (CAS No. 1241-94-7).

II. Tentative EPA Decision and Issues

A. Development of Rulemaking

The Agency has reviewed available data which indicate that human exposure to aryl phosphates as a category may be substantial; however, the ambiguous nature of the information available regarding changes in the production, use and subsequent human exposure to aryl phosphates, and the lack of reliable environmental monitoring data have prompted EPA to issue an Advance Notice of Proposed Rulemaking (ANPR) for the aryl phosphates, rather than issue a proposed test rule.

Should data be submitted which indicate that exposure levels are biologically insignificant or that the number of people exposed to the aryl phosphates is low, the Agency will reconsider its decision to proceed with this rulemaking action. EPA will, in the intervening period between publication of this ANPR and issuance of a proposed section 4(a) rule, attempt to refine the exposure data and reconsider its decisions in light of any additional data that become available.

EPA, in publishing this ANPR, wishes to receive comment on its tentative basis for requiring testing, and on the tests the Agency believes necessary to characterize the health and environmental effects of the aryl phosphates. The bases for the suggested findings, and for the tests under consideration, are discussed below.

B. Preliminary Findings

1. *Potential human exposure.* The Agency considers that publicly available information indicates that the nine aryl phosphates listed above may meet the criteria for a finding under section 4(a)(1)(B)(i): that the chemicals are produced in substantial quantities and that there is or may be substantial human exposure (see Table 1).

TABLE 1

Chemical	1977 production (mil. lb.) [1]	1980 projected production (mil. lb.) [2]	Used as plasticizer	Used as hydraulic fluid/ lubricant additive	Number of persons exposed in the workplace
TCP	23	[3]	X	X	187,709
TXP	15	[3]	X	X	3,165
TPP	16	10	X		7,631
NPDP/DBSP [4]	13	15-20	X	X	2,893
IPDP	28	30-40	X		669
BPDP	3	15-20	X	X	521
IDPP	10	15	X	X	N.A.
EHDP	3	4-6	X	X	[5] 11,432
Total	111	100-140			

[1] Refs. 42 and 50.
[2] Ref. 46.
[3] Confidential industry estimates show a substantial drop in production since 1977.
[4] Reported jointly by industry.
[5] Subject to regulation by FDA under 40 CFR Part 175.300; 380; 390; 176.170 and 177.1210

Most human exposure to aryl phosphates occurs in the workplace. The ITC cited the 1972-74 National Occupational Hazard Survey (NOHS), published in 1977 by the National Institute for Occupational Safety and Health (NIOSH) (Ref. 63), as one of their reasons for recommending testing of the aryl phosphates.

Aryl phosphates are used primarily as fire retardant plasticizers (36.5 million pounds in 1977), and as hydraulic fluids and lubricant additives (41.8 million pounds in 1977) (Ref. 42). Human exposure to aryl phosphates occurs primarily during polyvinyl chloride (PVC) processing and hydraulic fluid use.

About 90 percent of the 36.5 million pounds of aryl phosphates used as flame retardant plasticizers are used in the processing of polyvinyl chloride (Ref. 52). The remaining ten percent is used in various other plastics. No major difference in exposure profile would be expected due to the particular type of polymer in which the aryl phosphates are used. Certain procedures used to manufacture PVC products, such as calendering, roll coating, film casting, and dip molding, may afford opportunities for exposure to plasticizer mists containing aryl phosphates (Ref. 42).

Fire resistant hydraulic fluids (excluding brake fluids) based on phosphate esters are used primarily in applications where high temperature could pose a fire hazard if the hydraulic system developed leakage. The steel and automotive industries account for 65-70 percent of aryl phosphate hydraulic fluid uses (Ref. 42). Leakage of fire resistant hydraulic fluids containing phosphate esters may expose workers in the basic metals industries, the automotive industry, die casting operations and steel foundries, and military applications (Ref. 55). Evidence that such leakage is not infrequent is provided by estimates that as much as 80 percent of the annual use of phosphate esters in hydraulic fluids may be for replacement of losses (26.8 million pounds in 1977) (Ref. 55).

NIOSH estimated in the 1972-74 National Occupational Hazard Survey (NOHS) that up to two million workers may be exposed to aryl phosphates (Ref. 63). However, in the NOHS survey for the aryl phosphates, NIOSH made a "generic" estimate based on observations of products in general use in the workplace which the surveyor speculated might contain aryl phosphates. EPA believes that, in this instance, this "generic" NIOSH methodology may have overestimated actual aryl phosphate exposure by at least a factor of ten (Ref. 60). EPA believes that more recent NIOSH estimates, based on actual observed use of aryl phosphates and the presence in the workplace of tradename products known to contain aryl phosphates, are

more reliable, and has based its evaluation on those figures (Ref. 46). The actual and tradename results of the survey indicate substantial human exposure to some aryl phosphates. However, it is not clear that the actual and tradename survey results provide an accurate picture of human exposure due to changes in the market condition for aryl phosphates over the last 5 years (Table 1).

For instance, the production and use of TCP reportedly has declined dramatically since the 1972–74 NOHS was performed (Ref. 54). This decline has occurred as a result of the greater availability and economy of synthetic feedstocks and the intentional phase-out of TCP from certain uses due to the neurotoxicity of its ortho isomer (TOCP).

Manufacturers of TCP cite this decline as evidence that exposure to TCP has also declined dramatically. If exposure has decreased as much as production, it would be more than an order of magnitude lower than indicated by the 1972 NOHS and may not be considered substantial by EPA. However, manufacturers of TCP admit that their knowledge of some of the downstream uses of TCP is very limited and that it is possible that small amounts (several percent) of TCP could be added to various specialty lubricants or other similar products to which a substantial number of persons might be exposed (Ref. 54). The manufacturers believe that the health significance of such exposures would be minimal, but have been unable to date to fully support this contention. A new NIOSH survey is currently being conducted; however, results will not be available until at least 1984. The replacement of TCP by synthetic feedstock-derived aryl phosphates also raises the concern that the 1972–74 NIOSH survey may underestimate exposure to IPDP, NPDP, DBDP, IDPP, BPDP, and EHDP. If current exposure estimates for these six aryl phosphates indicate substantial TSCA-covered exposure, EPA would expect to make substantial exposure findings under section 4(a)(1)(B)(i) of TSCA for each of these aryl phosphates. (Exposure due to uses regulated under the Federal Food, Drug and Cosmetic Act are not covered by TSCA).

With the possible exception of TCP, significant direct consumer exposure is unlikely because other aryl phosphates do not appear to be in consumer products except as plasticizers. Because of the tendency of the aryl phosphates to remain bound within the polymer matrix, they are not expected to leach or volatilize from plastics in which they are contained in sufficient quantities to cause concern due to this mode of exposure (Ref. 42). The NOHS lists a number of products which contained TCP which might be expected to have consumer as well as industrial uses (Ref. 46).

As discussed under Unit B.3. of this Notice, Environmental Release, aryl phosphates are quite insoluble in water and would be expected to adsorb strongly to sediments (Ref. 41). Thus, any aryl phosphates released to the aquatic environment would be expected to partition to sediments and would not likely result in direct human exposure, such as in finished drinking water. However, the potential does exist for indirect human exposure as a result of aryl phosphates accumulating in sediment-bound organisms or organisms which filter-feed sediment and interstitial waters, which in turn may be consumed by humans as food (shrimps, clams, mussels, snails, etc.). The Agency has not seen any data which would suggest that significant exposure to aryl phosphates occurs via foods or drinking water, however.

2. *Adequacy of information and need for health effects testing.* EPA has approached its analysis of human health concerns for the aryl phosphates from the standpoint of both potential unreasonable risk (section 4(a)(1)(A)) and substantial production and exposure (section 4(a)(1)(B)). (See Table 2). The specific justifications for each approach are discussed below.

TABLE 2.—SUMMARY OF TENTATIVE HEALTH EFFECTS TESTING REQUIREMENTS

Effect	Under a 4(a)(1)(A) finding [1]	Under a 4(a)(1)(B) finding [2]
Chronic/subchronic	No	All.[3]
Mutagenicity	IPDP [4]	All.[3 4]
Oncogenicity	No	Triggered.[5]
Teratogenicity	TCP	All except NPDP, DBDP, TPP.
Reproductive	TCP	All.[3]
Neurotoxicity	IPDP,[6] TXP, TCP	IPDP,[6] TXP, TCP.
Epidemiology	No [7]	No.[7]

[1] "May present an unreasonable risk" finding.
[2] Substantial production and substantial or significant human exposure finding.
[3] All aryl phosphates meeting substantial production and exposure criteria.
[4] Ongoing industry testing meets testing needs of IPDP for gene mutations. If results are positive, EPA will propose higher tiered testing of IPDP to permit assessment of mutagenic risk. If substantial production and exposure criteria are met for IPDP, EPA will propose chromosomal abberations testing of IPDP.
[5] Testing requirement dependent upon results of mutagenicity and subchronic testing.
[6] Ongoing industry testing meets testing needs of IPDP for neurotoxicity.
[7] EPA does not believe a suitable study population can be identified at this time.

a. *Chronic toxicity.* Several subacute and subchronic studies have been conducted on various aryl phosphates, including TCP, TPP, DBDP, NPDP, and TXP (Refs. 17, 23, 44, 45, 47 and 51), but these are primarily oral neurotoxicity studies in the hen of 28 days or less duration, and are not adequate to assess the organ-specific subchronic effects in mammals for these aryl phosphates. Concentrations reported to produce effects in the liver, kidneys, and adrenals of rats resulting from inhalation for up to 90 days ranged from 450 ppm to 50,000 ppm with typical lowest effect levels reported at about 1,000 ppm (Ref. 47, 51). Although these results are consistent with the low acute toxicity of these compounds (Refs. 10, 23, and 49), the Agency believes that organ-specific studies of 90-day duration (or longer) in at least one mammalian species are needed to adequately assess the subchronic effect of any aryl phosphate to which there is substantial human exposure, and would propose subchronic testing under section 4(a)(1)(B) for all such aryl phosphates. However, the data available to the Agency up to this time do not support testing under section 4(a)(1)(A) (potential unreasonable risk).

b. *Mutagenicity.* All of the nine commercial aryl phosphates have received some mutagenicity testing using the Ames assay (Refs. 18–22, 30 and 49). Negative results were obtained for all of the aryl phosphates tested with the exception of IPDP. These assays are inadequate to completely characterize the mutagenic potential of the aryl phosphates, however, because the Ames test is not generally recognized as a stopping point in the tier testing of large exposure chemicals. Therefore, EPA is considering requiring that TCP, TXP, TPP, NPDP, DBDP, BPDP, IDPP, and EHDP be tested under TSCA section 4(a)(1)(B) for specific-locus gene mutation in cells in culture, for DNA damage as evidenced by either unscheduled DNA synthesis or sister chromatid exchange (SCE) formation, and for their ability to induce chromosomal aberrations in cells in culture. However, with the exception of IPDP, the data available to the Agency do not support testing under section 4(a)(1)(A) at this time.

Test results on IPDP were negative in the Ames test and negative without activation in the mouse mammalian cell gene mutation test using lymphoma cells (Ref. 49). However, IPDP results were equivocal with activation in the mouse lymphoma test. As a result, EPA believes an additional confirmatory gene mutation test is necessary for IPDP. Industry is conducting such a test which was initiated in April 1983 (Ref. 62). For this reason, EPA is not initiating section 4(a) rulemaking to require gene-mutation testing of IPDP at this time. Should the industry testing of IPDP or other data reveal a need for further mutagenicity testing of IPDP (including chromosomal abberration) which industry is unwilling to perform, EPA will reconsider the need for a section 4(a) test rule for mutagenicity for this substance. The protocol and design for the mutagenicity testing being conducted by industry are discussed in Unit III of this notice. If a substantial exposure finding is made for IPDP under section 4(a)(1)(B), the Agency would expect to propose chromosomal aberration testing.

c. *Oncogenicity.* EPA believes that human exposure to the aryl phosphates

may be substantial under section 4(a)(1)(B) by currently available information, but has not seen any data which would indicate that they may present an oncogenic risk under section 4(a)(1)(A). Therefore, for purposes of determining testing needs under TSCA section 4, the Agency believes that the mutagenicity testing outlined above, together with the organ-specific subchronic testing to be required for all aryl phosphates meeting substantial production and exposure criteria, provides a reasonable screening program to determine which, if any, of the aryl phosphates should be subjected to lifetime oncogenicity bioassays in laboratory animals. In accordance with that assessment, such testing would be required only if the results of the mutagenicity testing are positive or if the toxicity shown in the organ-specific subchronic testing indicates a likelihood of oncogenicity. However, EPA will continue to review this preliminary decision, and requests public comment on the issue of utilizing mutagenicity testing as a screen for identifying candidates for oncogenicity testing. (See Unit IV.). The Agency's rationale for planning to require a test system which would trigger oncogenicity testing from a mutagenicity test battery is based on a long history of scientific investigation as to the correlation between mutagenicity and carcinogenicity (Ref. 71).

Prior to the late 1960's and early 1970's, it was generally felt that there was little or no correlation between mutagenicity and carcinogenicity. Few mutagens had been shown to be potent carcinogens, and carcinogens which had been tested for mutagenicity, primarily in microbial assays which lacked the capacity for metabolic activation, has been designated "nonmutagenic." As basic understanding of the metabolism of carcinogenic chemicals increased, it was discovered that many carcinogens undergo metabolic activation to an ultimate carcinogenic moiety by mammalian enzyme systems. This discovery was followed by the development of an *in vivo* system, the host-mediated assay, to test for potential mutagenicity (Ref. 72); and *in vitro* testing of reactive forms of carcinogenic chemicals (Refs. 73–76) which resulted in a demonstration of the mutagenicity of many known carcinogens.

Whatever the mechanistic basis for the correlation between mutagenicity and carcinogenicity, there does appear to be an empirical correlation which is worth exploiting in the identification of potential carcinogens. The Agency currently believes that the correlations indicated by these data are sufficiently sound such that the carcinogenic potential of a chemical may reasonably be predicted from the results of a mutagenicity testing scheme for the purposes of setting priorities for conducting oncogenicity bioassays under section 4 of TSCA. The Agency requests public comment on this issue.

d. *Teratogenicity.* Some data are available relating to the teratogenic potential of triorthocresyl phosphate (TOCP), NPDP, DBDP, and TPP (Refs. 7, 44, 57, 58, 59). With the exception of TOCP, the results are sufficient to reasonably predict that these aryl phosphates do not act as potential teratogens. EPA therefore is not proposing to require teratogenicity testing on NPDP, DBDP and TPP.

The only available teratogenicity study on TCP (Ref. 59) does not adequately characterize the teratogenic potential of TCP because the protocol design is invalid and only the ortho isomer (TOCP) was tested. This study was intended as a preliminary study to examine the potential effects of prenatal exposure to TOCP on postnatal behavior. Therefore, TOCP was administered (at 500 and 750 mg/kg/day) by gavage late in gestation (day 18 and 19) during the fetal period. The investigators reported that significant increases in abnormalities were not observed. This is not surprising, however, because the most susceptible period to inducing gross structural abnormalities is during the period of major organogenesis (day 15–16 in the rat), and not the fetal period (Ref. 68). The Agency does not believe that the study provides reliable data upon which to evaluate the teratogenic potential of TCP.

Concern for the possible teratogenicity of TCP is supported by the suggestion that TOCP may interfere with vitamin E metabolism (see Unit II.B.2.e., Reproductive Effects, below); vitamin E deficiency during gestation produces severe and often lethal syndromes of congenital malformations in laboratory animals (Ref. 7). Thus, the Agency intends to require teratogenicity testing of TCP under section 4(a)(1)(A) of TSCA. Because the Agency lacks data on the teratogenicity of TXP, IPDP, BPDP, IDPP, and EHDP, it is considering proposing teratogenicity testing for these compounds under section 4(a)(1)(B) if there is substantial exposure to these compounds.

e. *Reproductive effects.* The reproductive effects of the aryl phosphates have not been adequately characterized. Therefore, the Agency is considering proposing reproductive effects testing under section 4(a)(1)(B) for all aryl phosphates for which there is substantial production and exposure. The only data available are for tricresyl phosphate (TCP) and are from a Russian study on the comparative gonadotropic effects of tricresol, phosphorous oxychloride, and tricresyl phosphate, and from a general toxicology study in which a species comparison was conducted.

The data from the Russian study (Ref. 69) indicated that inhalation exposure of rats to the MAC (maximum allowable concentration) of tricresyl phosphate did not cause any changes in the ovarian and estrus cycles. The actual concentration to which the animals were exposed was not included in the report.

In the general toxicology study conducted by Carpenter (Ref. 6), some degree of degeneration of seminiferous tubules was reported in three of four testes examined from twelve dogs which had been exposed to 20 subcutaneous injections over a 4 to 5-week period of a mixture of phosphate esters of cresols, xylenols, and other alkyl phenols (TCP). The dose levels at which these effects were observed were not explicitly stated, but the doses administered to a total of 12 dogs ranged from 100 to 500 mg/kg/dose. The study also reported that several rabbits which had been exposed to the same mixture by gavage exhibited changes suggestive of early testicular degeneration, but these changes were not definitive enough to be conclusive. The dose levels at which these effects were observed were not clearly indicated, but the doses administered to the six animals ranged from 120 to 480 mg/kg/day for 2 to 14 days or a total dose of 0.72 to 2.88 g/kg.

Because many of the toxicities observed following exposure to TCP were similar to those reported resulting from vitamin E deficiency, and because the structure of TCP appears to be similar to features of tocols possessing vitamin E activity, Carpenter suggested the possibility that interference with vitamin E metabolism may be responsible for toxic effects observed following exposure to TCP (Ref. 6).

In summary, these studies are inadequate to assess the reproductive effects of tricresyl phosphate. Some of the reasons are as follows: (1) The actual doses administered or at which adverse testicular effects were observed were not clearly indicated; (2) the number of animals on test were either too few or not reported; (3) the duration of exposure was either not reported or too short; (4) the dosing of dogs which showed evidence of testicular degeneration was performed by

subcutaneous injection, which is not representative of potential human exposure to TCP; and (5) neither study examined the effects on male and female reproductive performance, such as mating behavior, conception, parturition, lactation, weaning, and on the growth and development of offspring.

If TCP or TOCP, indeed, are vitamin E antagonists, their potential for inducing adverse reproductive effects should be of concern. Vitamin E is important in the maintenance of normal testicular function and is critical in the normal development of offspring. Interference with vitamin E metabolism may result in serious adverse reproductive effects (Ref. 7). Therefore, the Agency is considering proposing under section 4(a)(1)(A) that a 2-generation reproductive study be conducted on TCP.

Although the Agency believes that evidence of reproductive toxicity on one category member raises some suspicion of this hazard from the others, under 4(a)(1)(A) EPA would propose reproductive effects testing only on TCP at this time because of the weaknesses of the reproductive effects studies of TCP described above. If the results of the study on TCP are positive, EPA then proposes to trigger full reproductive effects testing under section 4(a)(1)(A) for all other category members.

f. *Neurotoxicity.* All nine aryl phosphates have been tested for acute toxicity by both oral and dermal routes (Refs. 1, 4, 6, 25–28, 31–34, 47, and 49) and the acute neurotoxicity of certain aryl phosphates (TCP, TXP, IPDP) is well documented (Refs. 33–37). With the exception of subchronic neurotoxicity of IPDP, TXP and TCP, all aryl phosphates have been adequately characterized with respect to neurotoxic potential (Refs. 2–4, 8–17, 24–28). In the case of IPDP, the Agency has concluded that acute testing was adequate to determine that the para and meta isomers are not potentially neurotoxic, and that ortho isomer is neurotoxic (Refs. 3, 8–11, 16, 23–27, 36–38). FMC corporation has agreed to perform a 90-day subchronic neurotoxicity study of commercial IPDP as discussed in Unit III of this notice. The results of this study will be sufficient to reasonably predict or determine the neurotoxicity of IPDP.

The 2,3- and 2,4- isomers of TXP have been shown to be neurotoxic, as well as the 2,4-2,4-3,5- and the 2,6-3,5-3,5-isomers (Refs. 33–37). EPA considers the existing studies on TXP inadequate to assess the chronic neurotoxicity of TXP because of the small numbers of animals tested, the limited duration of exposure, and the low levels of exposure to which the test animals were subjected. Because of the indications of neurotoxic potential and lack of adequate data, EPA expects to propose subchronic neurotoxicity testing of a commercial mixture of the isomers of TXP under TSCA section 4(a)(1)(A).

The Agency has concluded that, although data on the acute neurotoxicity of TCP are adequate, available data on the chemical's subchronic neurotoxicity are not. Some data do exist, but the studies reviewed by the Agency are studies on the hen of 28-day duration (Refs. 17, 28), which are not sufficient to adequately assess the effects of TCP over time for a subchronic neurotoxic effect. Industry's 90-day subchronic neurotoxicity study in the hen on isopropylphenyl diphenylphosphate (IPDP) (see Unit III. 2.) will use triorthocresyl phosphate (TOCP) as the positive control. The neurotoxic activity of TCP has been conclusively linked to its ortho isomer, TOCP (Ref. 33). Therefore, characterizing the subchronic neurotoxicity of TOCP should allow EPA to reasonably predict the subchronic neurotoxicity of TCP whose TOCP content is known. However, the use of TOCP as a positive control in the ongoing IPDP study will involve only one dose level; this will not permit the determination of a dose-response curve. Therefore, EPA expects to propose under TSCA section 4(a)(1)(A) a 90-day subchronic neurotoxicity study using three dose levels of TOCP. Analytical data on each manufacturer's commercial TCP product will allow the Agency to assess the potential toxicity of the commercial TCP product relative to the content of TOCP within that product. In addition, because the available data are inadequate for assessing the neurotoxicity of TXP and TCP, the Agency is considering proposing such testing under TSCA section 4(a)(1)(B) for these two aryl phosphates if the substantial production and exposure findings are met.

g. *Epidemiology.* EPA believes that an epidemiological study of workers exposed to aryl phosphates could potentially provide reliable data for evaluating the potential risk of neurologic harm from such exposure. EPA attempted to define a suitable study population through extensive contractor efforts. Excessive problems in terms of valid cohort identification were presented, however. The number of workers involved in manufacturing is too small to permit a valid study for the observation of neurotoxic effects, and the number of processors is so large as to present severe logistical problems. Further attempts to define a cohort were not recommended by the contractor (Ref. 53). Because of the difficulty in identifying a suitable study population, EPA has concluded that an epidemiological study is not feasible at this time and will not propose that an epidemiological study be undertaken.

3. *Environmental release.* In 1977 an estimated 26.8 million pounds of aryl phosphates in hydraulic fluids were used to replace losses due to leakage from pumps, primarily in the heavy metal and automotive industries (Ref. 42). The fate of such leakage may be aqueous discharge, landfill, and/or reclamation. Typically, each hydraulic machine has a catch basin or other device to catch and retain any leaks from the machine. These "catchings" are collected in a sump where the "oil" is separated from the water. The "oil" is collected for disposal or for reclamation. The water is usually filtered and sent to the sewer. This water is sometimes pretreated on the site before it is sent to publicly-owned treatment works. Due to the hydraulic fluids' usage patterns and certain monitoring data, EPA believes that there may be substantial entry of the aryl phosphates into the environment without treatment. (Refs. 39, 41, 48). Because industries that use hydraulic fluid containing aryl phosphates are situated near both saltwater and freshwater environments, EPA believes that release to both environments is possible. The manufacturers of the aryl phosphates question this conclusion. They state that it is unrealistic to assume that substantial amounts of hydraulic fluid enter natural aquatic systems without treatment. In support of their position, the aryl phosphates manufacturers submitted a monitoring study conducted by Monsanto which reported that there was a negligible or nonexistent release of aryl phosphates to the environment (Ref. 45). After careful review by EPA scientists, the Agency suggested that industry develop a new and more comprehensive monitoring and sampling protocol for the aryl phosphates. EPA did not believe that the original data submitted were adequate to support industry's position of little or no environmental release. In the Agency's view, the study submitted contained too few sampling sites, was conducted in a number of locations where the Agency considered detection of aryl phosphates unlikely, and did not provide a level of detection sensitive enough to adequately characterize the presence and extent of aryl phosphate contamination (Ref. 29).

To resolve the uncertainty regarding the amount of aryl phosphates released to the environment and the levels of aryl

phosphates in sediment and surface water, the Aryl Phosphate Industry Ad Hoc Committee agreed to conduct a monitoring study and submitted a monitoring protocol to EPA (Ref. 61). More recently, industry submitted the results of the completed aquatic monitoring study (Ref. 64).

Sample collection for this study began July 28, 1982, and the final report was received April 14, 1983 (Ref. 64). The protocol provided for sampling of all aryl phosphates at 24 sites mutually selected by EPA and industry where aryl phosphates were likely to be detected (such as downstream from hydraulic fluid production plants), as well as areas in which aryl phosphates have never been monitored but might be present (inner harbor at Baltimore, Md.). In addition, a sampling site was designated downstream from a major landfill where aryl phosphate production wastes are known to be disposed and several pristine sites were also included. Water and sediment samples taken from these sites were analyzed according to procedures set forth in Monsanto's Good Laboratory Practices Manual (Ref. 43).

Monsanto proposed a detection limit of 0.1 ppb for aryl phosphates in water. This detection limit is below the maximum acceptable toxicant concentration (MATC) for the most toxic aryl phosphate (DBDP) to the most sensitive species (rainbow trout) *viz.*, 0.8–1.4 ppb (Ref. 45). For aryl phosphates in sediments, Monsanto noted that current methodology would provide detection limits ranging from 30–200 ppb, and selected a detection limit ranging from 30–200 ppb, and selected a detection limit for aryl phosphates in sediment of 100 ppb.

However, upon receipt of the results of the monitoring study, Agency scientists noted several discrepancies in the quality assurance, analytical method, and statistical treatment of the data obtained. The Agency concluded that the data were ambiguous in certain details of statistical treatment (such as unspecified degrees of freedom for each entry in the data tables), that the results of the sediment data were particularly suspect, thereby necessitating further analyses, and that the field spiked sediment data did not support the lowest observed detection limit (LOD) of 100 ppb, (Refs. 65, 66, 67), as industry and EPA had agreed to in developing the original study protocol and design. For these reasons, the Agency believes that the study can not be relied upon to show that aryl phosphates are not present in the environment at levels of concern, and seeks comment through this ANPR as to the Agency's interpretation and analysis of the industry environmental monitoring study for the aryl phosphates in water and sediment.

In contrast to the suspected fate of aryl phosphates in hydraulic fluids, release from plasticizer use is predominantly as solid waste to landfills. The fate of such disposal is uncertain, but leaching of substantial quantities of aryl phosphates to surface waters or groundwater is unlikely because they adsorb strongly to soil, have low water solubility, and tend to remain in plastic materials (Refs. 41, 52).

The amount of aryl phosphates released from other sources is relatively low in comparison with the amounts from hydraulic fluid and plasticizer uses. Wastes from lubricant additive and miscellaneous uses appear to be promarily disposed of as solid waste and are primarily directed to landfills (Ref. 42).

4. *Environmental effects.* Although a great deal of environmental effects testing has been performed on the aryl phosphates, the environmental effects data base is not complete for all category members. For instance, a complete comparative toxicity data base for each aryl phosphate in a selected species is not available, nor has industry provided sufficient information to validate the majority of the existing studies. Some chronic aquatic toxicity and bioconcentration data exist for all aryl phosphates except TCP and TXP, although acute data exist for these two compounds (Ref. 45). Sufficient bioconcentration data exist to reasonably predict the bioconcentration potential of the aryl phosphates in fish, but not in benthic organisms (Ref. 45). Chronic aquatic toxicity data for algae or benthic organisms are generally lacking. The Agency and industry initially agreed that the toxicity data of the most toxic aryl phosphate (DBDP) to the most sensitive aquatic organism (rainbow trout) could be used to assess the risk of the aryl phosphate exposure to all organisms in the aquatic environment for those compounds for which data do not exist. Because DBDP was significantly more toxic to aquatic organisms than any of the other category members that have been tested, the Agency believed that an assessment based upon use of DBDP data would provide an ample margin of safety with respect to the potential hazard of other aryl phosphates.

However, the Agency has concluded that because the sediment detection limits, the quality assurance methods, the statistical treatment of the data generated, and the subsequent reliability of the monitoring study submitted by Monsanto are inadequate, more data are necessary to assess the no-observed-effect level (NOEL) and the subsequent environmental risk of aryl phosphates.

The Agency believes that these data can best be supplied by field monitoring studies which can evaluate whether or not trace concentrations of aryl phosphates are injurious to the environment. The most common approach used for such evaluations includes conducting acute and chronic toxicity tests with water, sediment, or soil collected from a contaminated area and a contiguous noncontaminated area. The presence of the contaminant(s) is the only known difference between these areas. Such studies can also be conducted in the field using a mobile testing unit. Such evaluations have also used in-stream cage toxicity and bioconcentration tests with fish and macroinvertebrates, and comparisons of: species diversity and abundance in water column and sediments; of standing crop (biomass); of ecosystem processes such as photosynthesis/respiration rates; and of colonization and decolonization of natural and artificial substrates. Such methods have been used by Monsanto, other chemical companies, the electric power industry, and others to test effluents. As such, the methods are considered by industry and the Agency to be readily available and standard practice (Ref. 70).

A further advantage of this testing approach over conventional laboratory testing is the ability of the tests to indicate the extent to which the toxicity of these nine aryl phosphates is additive with each other and is multiplicative (synergistic) with other environmental contaminants such as malathion and parathion. It is known that certain aryl phosphate compounds, when used as pesticides, exhibit this multiplicative effect in the presence of contaminants such as malathion and parathion, primarily due to the reactivity of their thiol groups (Refs. 77, 78). As such, the Agency is reexamining the adequacy of comparing the rainbow trout MATC for DBDP independently with the concentration of each aryl phosphate measured in the water column or calculated in the sediment interstitial water to gauge environmental risk potential (the "ester by ester" approach proposed by Monsanto (Refs. 65, 66, 67). To address this uncertainty, the Agency intends to propose supplemental testing under section 4(a)(1)(B) of TSCA, including tissue residue analysis of biota exposed to water and sediments collected from sites known to contain aryl phosphates at measurable levels. In

this manner, the additive or synergistic effect of the aryl phosphates with other environmental contaminants such as pesticides can be further elucidated.

Because of the soil adsorption characteristics of the aryl phosphates and their tendency to remain bound in landfill-disposed plastic wastes, it is unlikely that they would present significant direct exposures to terrestrial organisms (Refs. 42, 55). However, the recent disposal practices employing estuarine dredge spoils, river sludge and stream tailings as sources of fertilizer and soil adjuvants on crop lands and reclamation sites may provide a source of significant exposure to terrestrial organisms. Therefore, EPA is considering initiating rulemaking under section 4(a)(1)(B) at this time to require testing for effects on terrestrial organisms. Having described these types of available field studies, the Agency seeks comments through this ANPR as to which of these testing methods would be most appropriate for assessing the environmental effects of aryl phosphates.

III. Industry Testing

1. *Mutagenicity.* FMC Corporation has submitted protocols (Ref. 62) to characterize the mutagenic potential of isopropyhenyl diphenyl phosphate using the six-linked recessive lethal (SLRL) mutagen assay in *D. melanogaster* after the method of Brusick (Ref. 5). Accumulated evidence has shown this test to be the most sensitive among different test systems in *D melanogaster* (Ref. 56). The test measures the frequency of lethal mutations in approximately one-fifth of the total genome of the fly. Testing began in April 1983 and a final report should be available to EPA early in 1984. The protocol called for exposure of at least 200 adult male files to two dose levels of the test substance and use of both negative and positive controls. A commercial grade of IPDP is being tested. This test is being performed concurrently with the subchronic neurotoxicity study described below. If the result of this test is negative, no further gene mutation testing will be proposed according to the standard TSCA section 4 mutagenicity testing sequence. If the results are positive, EPA will propose additonal testing of IPDP to permit assessment of mutagenic risk.

2. *Subchronic neurotoxicity.* FMC Corporation is currently conducting a 90-day subchronic neurotoxicity study in the hen to provide data on the neurotoxicity of IPDP under the testing guidelines set forth for testing under the Federal Insecticide, Fungicide, and Rodenticide Act (43 FR 37374) which specify negative and positive controls and three dose levels. Triorthocresyl phosphate is being used as the positive control. The hen was selected as the test species because there are entensive background data on the hen and studies indicate that hens and humans have similar sensitivities to neurotoxic organophosphates (Refs. 36, 40). The birds will be examined daily for signs of ataxia. At the conclusion of the 90-day period, the birds will be sacrificed and examined histologically for neural lesions.

3. *Other provisions of testing agreements.* Industry has agreed to adhere to the proposed TSCA Good Laboratory Practice Standards published by the Agency, (44 FR 27334, May 9, 1979, 45 FR 77332, Nov. 21, 1980) and has agreed to permit laboratory audit inspections in accordance with the procudures outlined in TSCA section 11, at the request of authorized representatives of the EPA. These inspections may be conducted for purposes which include verification that testing has begun, that schedules are being met, that reports accurately reflect the raw data, and that the studies are being conducted with adequate quality assurance procedures.

In addition, industry has agreed that all raw data, documentation, records, protocols, specimens, and reports generated as a result of a study will be retained as specified in the proposed TSCA Good Laboratory Practice Standards published by the Agency and will be made available during an inspection or submitted to EPA if requested by EPA or its authorized representative.

Industry has agreed that TSCA section 14(b)(1)(a)(ii) governs Agency disclosure of all test data submitted pursuant to these studies.

4. *Timing of testing.* Industry began both the proposed 90-day subchronic neurotoxicity and mutagenicity tests of April 1, 1983. Final reports will be submitted to EPA within 12 months of study initiation for subchronic neurotoxicity, and within 9 months for mutagenicity.

IV. Issues for Comment

1. One of the reasons given for the decline in production of TCP, the aryl phosphate indicated by the 1972–74 NOHS to be of greatest exposure concern, is the substitution of aryl phosphates made from synthetic feedstocks. This may mean that the exposure to aryl phosphates made from synthetic feedstocks is considerably greater than the 1973–74 NIOSH survey indicates. How many persons are exposed to these aryl phosphates and what is the nature of the exposures? Are any new uses expected for any of these substances? What is the projected market growth rate for these substances over the next five years? Did any notable changes occur in the production volume of the individual substances over the last five years?

2. EPA expects to propose a 90-day subchronic neurotoxicity study for TCP, using 3 dose levels. EPA favors testing TOCP. Will the analytical data received from the manufacturers of commercial TCP relative to the TOCP content of their commercial product, when combined with the results of EPA's proposed 90-day subchronic neurotoxicity study using 3 dose levels of TOCP, enable the Agency to reasonably determine or predict the neurotoxicity of a TCP commercial product?

3. Should subchronic neurotoxicity testing of TXP be required based upon indications that certain TXP isomers are acutely neurotoxic and the potential for TXP exposure through use in consumer products?

4. Do data implicate only TOCP as responsible for the suggested reproductive and teratogenic effects of TCP? Should individual TCP isomers be tested separately? Do the existing data for TOCP provide sufficient evidence to indicate that the other aryl phosphates might cause teratogenic or reproductive effects?

5. If there is substantial human exposure to a number of aryl phosphates, considerable testing would be necessary to characterize the toxicity of each individual aryl phosphate. Is there a way to reduce this testing burden by testing a subset of the aryl phosphates, either by forming subcategories of similar aryl phosphates or by testing a subset which spans the structural spectrum of the aryl phosphates category?

6. EPA believes the monitoring studies performed by Monsanto were inadequate to demonstrate that aryl phosphates are not present in the environment at levels which may present a risk to aquatic life. EPA seeks comment on the criteria upon which the Agency based its evaluation of the results of the monitoring study, such as the detection limit sensitivity, quality assurance evaluation, location and selection of sampling sites, statistical treatment of the data obtained, analytical method, and the interpretation of the results.

7. Because monitoring data alone will not allow the calculation of a no-observed-effect level (NOEL), the Agency is considering issuing a site-

specific test protocol for aquatic environmental effects testing for the aryl phosphates which would employ water and sediment actually taken from designated sampling sites, with tissue sample analysis for aquatic and benthic organisms cultured in these media. Is this approach appropriate or should standard ecotoxicity testing protocols be used to fill in missing information? If site-specific testing is performed, which organisms should be cultured in order to best quantify the levels of aryl phosphates in water and sediment? Should ecotoxicity testing for terrestrial organisms be proposed, in addition to aquatic toxicity testing, in order to more accurately evaluate the effect of aryl phosphates on the environment?

8. Should oncogenicity testing of the substantial exposure aryl phosphates be required only if the selected mutagenicity tests produce non-negative results, or should oncogenicity testing of these compounds be required immediately on the basis of TSCA section 4(a)(1)(B) findings?

VI. References

(1) Aizenshtadt, vs. 1969. Toxicology of vat residue of tricresylphosphate. Sb. Nauch. Tr. Kulbyshev. Nauch-Issled. Inst. 68, 92–93.

(2) Aldridge WN. 1954. Tricresylphosphate and cholinesterase. Biochem J. 56:185–9.

(3) Aldridge WN, Barnes JM. 1961. Neurotoxic and biochemical properties of some triaryl phosphates. Biochem. Pharmacol. 6:177–188.

(4) Bondy HF et al. 1960. A study on the acute toxicity of the triaryl phosphates used as plasticizers. Brit. J. Industri. Med. 17:190–200.

(5) Brusick, D. J. 1980. Principles of Genetic Toxicity. Plenum Press, New York, NY.

(6) Carpenter, HM, et al. 1959. Toxicology of a triaryl phosphate oil. I. Experimental toxicology. A.M.A. Arch. Ind. Health. 20:234–252.

(7) Draper, HH, James, MF. and Johnson, BC. 1952. Tri-o-cresyl phosphate as a vitamin E antagonist in the lamb and rat. Fed. Proc. 11, 204.

(8) FMC. 1969a. January 8. Subacute oral neurotoxicity study of MP–600.

(9) FMC. 1969b. January 8. Subacute oral neurotoxicity study of Kronitex 200.

(10) FMC. 1976. January 29. Acute toxicity screening tests Kronitex 50: synthetic triaryl phosphate, ICD/T–76–014. TRDB–0780–003.

(11) FMC. 1977a. September 15. Oral neurotoxicity study of Kronitex 200 B. ICG/T–77–110.

(12) FMC. 1977b. May 5. Oral and dermal neurotoxicity study of Kronitex TXP. ICD/T–77–062.

(13) FMC. 1977c. June 13. Oral neurotoxicity study of Kronitex 50. ICG/T–77–079.

(14) FMC. 1977d. June 13. Oral neurotoxicity study of Kronitex 100. ICG/T–77–080.

(15) FMC. 1977e. September 15. Oral neurotoxicity study of Kronitex 200. ICG/T–77–109.

(16) FMC. 1977f. June 13. Oral neurotoxicity study of Kronitex 300. ICG/T–77–081.

(17) FMC. 1977g. May 5. Oral and dermal neurotoxicity of Kronitex TCP. ICG/T–77–061.

(18) FMC. 1978a. November 17. Mutagenicity screening test: *Salmonella*/microsomal assay of Kronitex TCP (C–8824–29). ICG/T–78–151. TRDB 0780–005.

(19) FMC. 1978b. November 15. Mutagenicity screening test: *Salmonella*/microsomal assay of Kronitex TXP (C–8824–23). ICG/T–78–147. TRDB 0780–005.

(20) FMC. 1978c. January 9. Kronitex 200B. Mutagenicity screening test: *Salmonella*/microsomal assay (Ames test). ICG/T–78–008. TRDB 0780–005.

(21) FMC. 1978d. October 13. Mutagenicity screening test: *Salmonella*/microsomal assay of trixylenyl phosphate ester (MP–600). Lot =77–1. ICG/T–78–114. TRDB 0780–005.

(22) FMC. 1978e. January 9. Kronitex 100B. Mutagenicity screening test: *Salmonella*/microsomal assay (Ames test). ICG/T–78–005. TRDB 0780–005.

(23) FMC. 1978f. April 24, 1978. Oral neurotoxicity of Kronitex TXP. =FCC7/79333. (Unpublished Report)

(24) FMC. 1979a. April 24, 1979. Oral toxicity of MP 600. =FCC7/79332. (Unpublished Report)

(25) FMC. 1979b. April 24, 1979. Oral neurotoxicity of Kronitex 50. =FCC7/79331. (Unpublished Report)

(26) FMC. 1979c. April 24, 1979. Oral neurotoxicity of Kronitex 100. =FCC7/79329. (Unpublished Report)

(27) FMC. 1979d. May 3, 1979. Oral neurotoxicity of Kronitex 200. =FCC7/79330. (Unpublished Report)

(28) FMC. 1979e. August 14, 1979. Oral neurotoxicity of Kronitex TCP 5479–78a. (Unpublished Report)

(29) USEPA. 1982. February 5. Memo from Kevin McCormack to aryl phosphates docket file. Minutes of December 8, 1981, meeting with industry concerning monitoring protocol design.

(30) Hanna PJ, Dyer KF. 1975a. Mutagenicity of organophosphorous compounds in bacteria and *Drosophila*. Mutat. Res. 28:405–420.

(31) Hegyvary C., Csalay L., 1963. Endocrinological aspects of poisoning with tri-o-cresyl phosphate. Endokrinologie 44, 62–67.

(32) Henschler D. 1958. Die Trikresylphosphatvergiftung: Experimentelle Klarung von Problemen der Atiologie and Pathogenese. Klin. Wschr. 36, 663–674.

(33) Henschler D, Bayer HH. 1958. Toxikologische Untersuchungen uber Triphenylphosphate und Triaryl phosphate aus Mischunger homologer Phenole. Naunyn-Schemedebergs Arch. exp. Path. Pharmak. 233, 512–517.

(34) Henschler D. 1959. Beziehungen zwische chemischer Strucktur und Lahmungswirkung von Triarylphosphaten. Naunyn-Schmedeberg Arch. Exp. Path. Pharmak. 237, 459–472.

(35) Hine CH., et al. 1956. The neurotoxicity and anticholinesterase properties of some substituted phenyl phosphates. J. Pharmacol. Exp. Therap. 116, 227–236.

(36) Johnson MK. 1975a. The delayed neuropathy caused by some organophosphorus esters: mechanism and challenge. CRC Critical Reviews in Toxicology pp. 289–316.

(37) Johnson MK. 1975b. Organophosphorous esters causing delayed neurotoxic effect. Arch. Toxicol. 34, 259–288.

(38) Johnson MK. 1975c. Structure-activity relationships for substrates and inhibitors of hen brain neurotoxic esterase. Biochem. Pharmacol. 24:747–865.

(39) Lombardo P, Egry I. 1979. Identification and gas liquid chromatographic determination of aryl phosphate residues in environmental samples. J. Assoc. Off. Anal. Chem. 62:47–51.

(40) Lotti M, Johnson MK. 1978. Neurotoxicity of organophosphorus pesticides: predictions can be based on *in vitro* studies with hen and human enzymes. Arch. Toxicol. 41:215–221.

(41) Mayer FL, Adams WJ, Finley MT, Michael PR, Mehrle PM, and Saeger VW. 1980. Phosphate ester hydraulic fluids: an aquatic environmental assessment of Pydraul 50E and 115E. Presented at ASTM Aquatic Symposium and submitted to EPA by Monsanto on March 6, 1980.

(42) Midwest Research Institute. 1979. May 15. Assessment of the need for limitation on triaryl and trialkylaryl phosphates. Draft Final Report. EPA Contract No. 68–01–4313 (MRI Project No. 4309–L).

(43) Monsanto. 1979a. Good Laboratory Practices Manual.

(44) Monsanto. 1979b. Dec. 14 Letter to Dr. Carol Mapes from Monsanto with enclosures. TRDB 0780–010.

(45) Monsanto. 1981. August 7 letter from William J. Adams to Steven D. Newburg-Rinn with enclosures.

(46) NIOSH. 1980. August. Quarterly hazard summary report.

(47) Saito C., et al. 1974 Tests of the subacute toxicity of tricresylphosphate (TCP) in rats. Oyo Yakuri 8:107–118.

(48) Sheaffer KK. 1977. November 14. Chief Aquatic Field Services Unit, Pennsylvania Department of Environmental Resources. Toxicity of aryl phosphates found in Kishacoquillas Creek, Pennsylvania. (Letter to PH Howard, Syracuse Research Corporation).

(49) Stauffer Chemical Company. 1979. December 17. Toxicology data summaries and test protocols for stauffer Chemical Company aryl phosphates, i.e., t-butyl phenyl diphenyl phosphates, tricresyl phosphate, trixylenyl phosphate, mixed tri-aryl phosphate, and isopropyl phenyl diphenyl phosphate. TRDB 0780–009.

(50) Stauffer Chemical Company. 1980. Projected aryl phosphate production estimates for 1980.

(51) Sutton WL et al. 1960. Studies on the industrial hygiene and toxicology of triphenyl phosphate. Arch. Environ. Health. 1:33–58.

(52) Touchette NW. 1978. Plasticizers. Modern Plastics Encylopedia. 1978–1979. 55(IOA):212

(53) USEPA. 1981. Sept. 28. Memo from Jason Toth to Irwin Baumel. Recommendations concerning aryl phosphates and implementation of section 4 test rules.

(54) USEPA. 1982. May 27. Personal communication between Kevin B. McCormack (EPA) and Harold K. Latourette (FMC Corporation). (Constitutes Confidential Business Information.)

(55) Versar Inc. 1980. Untitled draft report on aryl phosphates. Washington, D.C.: Office of Toxic Substances, U.S. Environmental Protection Agency, Contract No. 068-01-5791.

(56) Wurgler FE, Sobels FH, Vogel E. 1977. *Drosophila* as assay system for detecting genetic changes. In: Handbook of mutagenicity test procedures. Kilbey BJ, et al. eds. Amsterdam: Elsevier/North Holland Biomedical Press, pp. 335-373.

(57) Cavanaugh JB. 1983. Peripheral neuropathy caused by toxic agents. Crit. Rev. Toxicol. 2,365-417.

(58) McLaughlin J, Marliac JP, Verret MJ, Mutchler MK, Fitzhugh OG, Garth, O. 1963. The injection of chemicals into the yolk sac of fertile eggs prior to incubation as a toxicity test. Toxicol. Appl. Pharmacol. 5:760-771.

(59) Mele JM, Jensh RP. 1977. Teratogenic effects of orally administered tri-o/cresyl phosphate on Wistar albino rats. Teratol. 15:32A.

(60) USEPA. 1982. September. Personal Communication between Kevin B. McCormack (EPA) and David Sundin (NIOSH), Cincinnati, Ohio.

(61) Monsanto. 1982. Phosphate ester surveillance sample collection method. Report No. ES-82-M-1. Project No. 43-000-760.26. Dated January 28, 1982.

(62) FMC. 1981a. Protocols for sex-linked recessive lethal mutagenicity test in *Drosphila melonogaster* and subchronic neurotoxicity test in the hen. Letter from Tito Casieri (FMC) to Steven D. Newburg-Rinn (TRDB), with enclosures. Dated November 24, 1981.

(63) National Occupational Hazard Survey (NOHS) Vol. II. 1977 DHEW (NIOSH) Pub. NO. 77-213.

(64) Final report of the 1982 industry-EPA phosphate ester aquatic surveillance program. April 14, 1983. Submitted by Monsanto Company.

(65) USEPA. 1983. May 31. Memo to Steven D. Newburg-Rinn, from James Gilford. Review of aryl phosphates monitoring report.

(66) USEPA. 1983. May 18. Memo to Steven D. Newburg-Rinn from Joseph Carra. Review of aryl phosphates sampling and analysis results.

(67) USEPA. 1983. June 13. Memo to Robert Booth from Denis L. Foerst. Review of final report of the 1982 industry-EPA Phosphate Ester Aquatic Surveillance Program.

(68) USEPA. 1982. Oct. 28. Memo to Joseph J. Merenda from Irwin Baumel. TCP testing needs.

(69) Pashkova, GH. 1973. Comparative evaluation and general toxic effect of tricresol, phosphorous oxychloride, and tricresyl phosphate. Vopr. Gig. Tr. Profpatol Toksikol Proizvod Ispol's Fosforog Plastif 1975, 86-90.

(70) Kimerle, RA., et al. A tiered approach to aquatic safety assessment of effluents. (In press). Society of Environmental Toxicology and Chemistry. Pergamon Press.

(71) USEPA. 1982. Analysis of limited bioassays as potential carcinogenicity screening tests. EPA 68-01-6198.

(72) Gambridge, MG, Legator, MS. 1969. A host-mediated bioassay for the detection of mutagenic compounds. Proc. Soc. Exptl. Biol. Med. 130:831-834.

(73) Ames BN, Gurney FG, Miller JA, Bartoch H. 1972a. Carcinogens as frameshift mutagens: Metabolities and derivatives of acetyl aminofluorene and other aromatic amine carcinogens. Proc. Nat'l. Acad. Sci. USA, 69:3128-3132.

(74) Ames BN, Sims P, Grover PI. 1972b. Epoxides of polycyclic hydrocarbons are frameshift mutagens. Science 176:47-49.

(75) Huberman E, Aspiras L, Heidelberger C, Grover PL, Sims P. 1971. Mutagenicity to mammalian cells of expoxides and other derivatives of polycyclic hydrocarbons. Proc. Nat'l. Acad. Sci. USA 68:3195-3199.

(76) Huberman E. Donovan PJ, DiPaolo JA. 1972. Mutation and transformation of cultured mammalian cells by N-acetoxy-N-2-fluorenyl-acetamide. J. National Cancer Institute. 48:837-840.

(77) Hassan A, Dauterman WC. 1968. Studies on optically active isomers of 0,0-diethyl malathion and 0,0-diethyl maloxon. Biochem. Pharmacol. 17:1431-1439.

(78) Dyte CE, Rowlands DG. 1967. Specificity of insecticide synergists. Proc. Brit. Insectic. Furigi. Conf. pp. 344-354.

VI. Public Record

The EPA has established a public record for this testing decision (docket number OPTS-42038) which is available for inspection in the OPTS Reading Room from 8:00 a.m. to 4:00 p.m. Monday through Friday (except legal holidays) in Rm. E-107, 401 M St., SW., Washington, DC 20460. The record includes the following information:

(1) Federal Register notice containing the designation of the aryl phosphates to the priority list and all comments on aryl phosphates received in response to that notice.

(2) Communications, consisting of letters, contact reports of telephone conversations, and meeting summaries of Agency-industry and Agency-public meetings.

(3) Industry testing protocols and methods:

(a) Monsanto Good Laboratory Practices Manual (Environmental Analysis Laboratory).

(b) Monsanto Good Laboratory Practices Manual (Environmental Assessment Laboratory).

(c) Monsanto Standard Operating Procedure for determination of sample stability under conditions of preservation and storage.

(d) Monsanto Stability Study of Natural Sediment Samples Preserved by Frozen Storage.

(e) Monsanto Standard Operating Procedure for Homogenizing, Subdividing and Preserving Sediment Samples.

(f) Monsanto Standard Practice for Determination of Sorption Constants in Soil and Sediments.

(g) FMC Protocols for Sex-Linked Recessive Lethal Mutagenicity Test in *Drosophila melanogaster* and Subchronic Neurotoxicity Study in the Hen.

(h) Final Report of the 1982 Industry-EPA Phosphate Ester Aquatic Surveillance Program.

(4) Published and unpublished data.

The public record enumerated above includes basic information considered by the Agency in developing this decision. The Agency will supplement the record periodically with additional relevant information received.

(Sec. 4, 90 Stat. 2003; (15 U.S.C. 2601))

Dated: December 21, 1983.

William D. Ruckelshaus,

Administrator.

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